Immediate Placement of Implants into Periodontally Infected Sites in Dogs: A Histomorphometric Study of Bone-Implant Contact

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Purpose: *The placement of implants allows for re-establishment of function and esthetics following tooth loss. Immediate implant placement is a relatively recent procedure and has advantages, such as reduced number of surgical procedures, preservation of alveolar bone, reduction of cost and period of edentulism, and increased patient acceptance. However, there are some specific contraindications for the technique, such as the presence of an infection caused by periodontal disease and periapical lesions. The objective of this study was to evaluate the percentage of bone-implant contact of immediate implants placed in periodontally infected sites.* ***Materials and Methods:*** *In the first phase, periodontitis was induced with ligatures in the mandibular premolars of 5 mongrel dogs, using the contralateral teeth as controls (received prophylaxis only). After 3 months, in the second phase of the study, 40 implants were placed in the alveoli of both experimental and control teeth. After a healing period of 12 weeks, the animals were euthanized, and the hemimandibles were removed, dissected, fixed, and prepared for histomorphometric analysis of percentage of bone-implant contact. The Mann-Whitney test was used for statistical analysis.* ***Results:*** *The results of the histomorphometric analysis indicated mean bone-implant contact of 62.4% in the control group and 66.0% in the experimental group, a difference that was not statistically significant.* ***Discussion:*** *Histomorphometric results revealed similar bone-implant contact in both groups, with no signs of infection.* ***Conclusions:*** *It was concluded that periodontally infected sites may not be a contraindication for immediate implantation in this animal model system, if adequate pre- and postoperative care is taken.* (Int J Oral Maxillofac Implants 2003;18:391–398)

Key words: *dental implants, immediate dental implantation, induced periodontitis, infection, osseointegration*

Conventional endosseous implant protocol recommends a waiting period of up to 6 months after tooth extraction before implant placement. This delay is associated with inevitable postextraction bone loss, which can contribute to insufficient bone for implant placement and a long treatment period.

Immediate placement of root-form implants was first described by Schulte[1] after 8 years of follow-up in humans. This technique was developed so that problems related to conventional implant placement would be minimized or eliminated.[2–7] Immediate implant placement is as safe and efficient as conventional placement,[8–10] with apparent osseointegration even in different anatomic areas.[11,12] Preservation of bone height allows the placement of longer implants in the posterior maxilla, avoiding an additional surgical procedure to reconstruct the bone volume lost during healing.[13] Immediate implant healing, with or without guided bone regeneration (GBR), can present a similar Plaque Index, degree of gingival recession, and clinical attachment level as conventionally placed implants,[14] confirming the

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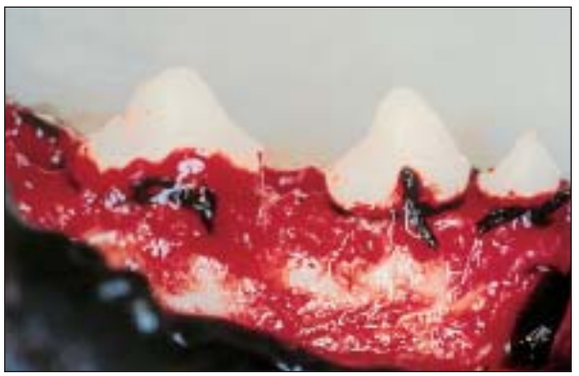

Fig 1 A silk suture is placed into an infrabony pocket created around premolar teeth.

success rate reported by Watzek and coworkers[15] when they placed implants to replace residual roots.

The advantages of immediate implant placement are: elimination of the waiting period for regeneration of the extraction sockets; maintenance of alveolar dimension; fewer surgeries; decreased toothless period, which reduces cost and increases patient acceptance[12,14,16]; and potentially better axial placement, esthetics, and subsequent biomechanical prosthetic restoration.

Schwartz-Arad and Chaushu[10] consider immediate implants contraindicated when there is purulent exudate present; bone loss to the apex; intimate contact with certain anatomic structures, such as the mandibular canal, maxillary sinuses, or nasal cavity; or clinical conditions that prevent primary flap closure. Although some consider infected sites a contraindication, Novaes Jr and Novaes[17] reported that success can be achieved if certain clinical pre- and postoperative measures are followed, such as antibiotic administration, meticulous cleaning, and alveolar debridement before surgery. Primary flap closure is also desirable when placing immediate implants, and surgical techniques to extend the flap and reduce or avoid exposure of the implant must be considered.[18]

Immediate implant placement can be contraindicated in the presence of periapical and periodontal lesions.[16,19–22] However, Novaes Jr and associates,[23] in a histomorphometric evaluation of immediate implant placement in dogs with induced periapical lesions, reported that osseointegration occurred in both experimental and control sites. According to these authors, immediate implant placement in the presence of periapical endodontic lesions is not contraindicated if appropriate therapy is carried out. However, immediate placement in periodontally infected extraction sites needs to be studied more comprehensively.

This investigation evaluated histomorphometrically the percent of bone-implant contact of immediate implants placed into periodontally infected alveoli in dogs.

MATERIALS AND METHODS

Five young adult male mongrel dogs, weighing approximately 10 kg each, were used in this study. The animals had intact maxillae, atraumatic occlusion, and no oral viral or fungal lesions, and they were in good general health, with no systemic involvement. The procedures were in accordance with guidelines approved by the Council of the American Psychological Society (1980) for the use of animal experiments and were divided into 2 phases.

Phase I

The dogs were not fed the night before the surgical procedure. They received 2% Rompun (Bayer, Porto Alegre, RS, Brazil; 20 mg/kg at the dosage of 0.5 mL/10 kg intramuscularly); and were then anesthetized with 1 mL/kg thiopental (Cristália Laboratory, Itapira, SP, Brazil; 20 mg/kg Thiopental, diluted in 50 mL saline intravenously).

Surgery was carried out by quadrants in each animal. In the first, second, third, and fourth mandibular premolars on the control side, the teeth received prophylaxis only. The contralateral side was used as the experimental group, where periodontitis was induced according to the technique of Schliephake and Kracht.[24] In summary, a nonresorbable silk suture was placed into infrabony pockets of approximately 1 mm in depth, which were created around each premolar after dissection of the marginal periodontium (Fig 1). After repositioning of the periodontal flaps, the wound was closed with resorbable sutures. The silk sutures were left in place for 3 months, during which time the animals were examined clinically every 4 weeks. At the end of 3 months, radiographs were taken to confirm the loss of alveolar bone height. Since the purpose of this phase was to induce periodontal infection, no prophylactic measures were taken.

Phase II

After 3 months of periodontal disease induction, the ligatures were removed. Attachment loss was observed clinically, which resulted in an increase of probing pocket depth and exposure of the bifurcations. The root surfaces were not cleaned, and granulation tissue was not removed.

Periodontal infection was confirmed by the presence of deep periodontal pockets, bleeding on

probing, exudation after soft tissue compression, and radiographic evidence of bone loss and furcation involvement. After confirmation of periodontal disease at the experimental sites, the animals were anesthetized in the same manner as described in phase I of the experiment. The night before the second surgery, the animals received 20,000 IU penicillin and 1.0 g streptomycin/10 kg body weight intramuscularly (Pentabiótico Veterinário de Pequeno Porte, Wyeth Laboratory, São Bernardo do Campo, SP, Brazil). Because each dose provided antibiotic coverage for 4 days, another dose was injected 4 days later, for a total of 8 days of antibiotic coverage. This is a broad-spectrum antibiotic commonly used to treat infections in small animals[23] and has a systemic and local effect on the control of the periodontal infection.

Full-thickness flaps were created on the experimental and control sides in the area of the first to fourth mandibular premolars. The teeth were sectioned in a buccolingual direction at the bifurcation, so that the roots could be individually extracted without damaging the bony walls. After extraction, the sites were meticulously debrided following a protocol previously described,[17] which involved curettage of the alveoli to remove all soft tissue tags and to stimulate resorption of the cortical lining, so as to expose the marrow cavities.

The sites were then irrigated with a 50 mg/mL solution of tetracycline hydrochloride, and Frialit-2 implants (Friadent, Mannhein, Germany) with a grit-blasted/acid-etched surface, 4.5 mm in diameter and 8 mm in length, were placed immediately (4 implants each side; n = 40 implants total). The implants were placed according to the manufacturer's instructions, and flaps were sutured with resorbable sutures. The implants used are well suited for immediate implantation since they are rootlike in shape, ie, they are wider cervically to adapt clinically to the alveolar walls and taper apically so that smaller amounts of bone need to be removed during site preparation. The animals were maintained on a soft diet for 14 days. Healing was evaluated periodically, and the teeth were cleaned monthly with ultrasonic points.

The animals were sacrificed with an overdose of thiopental 12 weeks after implant placement. Hemimandibles were removed, dissected, and fixed in 4% phosphate-buffered formalin (pH 7) for 48 hours and transferred to a solution of 70% ethanol until processing. The specimens were dehydrated in increasing concentrations of alcohol up to 100%; infiltrated and embedded in resin (LR White, London Resin Company, Berkshire, England); hard-sectioned using the technique described by Donath and Breuner[25]; and stained with Stevenel's blue and Alizarin red S.

Histomorphometric Analysis

One longitudinal histologic mesiodistal section from each implant was evaluated, in accordance with several authors,[26–29] using an optic microscope (Axiophot, Zeiss, Oberkochen, Germany) at 50× magnification. The microscopic images were captured by a videocamera (Sony CCD-IRIS, Sony Electronics, San Jose, CA) and digitized by a video grabber (Snappy, Play, Rancho Cordova, CA). Morphometry software (MetaMorf, Universal Imaging, West Chester, PA) was used to analyze the sections. With this system, the percent of implant-bone contact was determined from the middle third of the implants in accordance with Novaes Jr and associates[23] and Evans and colleagues.[30] The middle third of the implants was analyzed purposely to avoid the cervical third, because of possible resorption of the bone crest, and the apical third, because implants could closely approximate or slightly penetrate the superior wall of the inferior alveolar canal. The measurements started 2 mm below the bone margin, an area still possibly affected by the induced infection, because the anaerobic bacteria and their products induce a complex immune and inflammatory process within the periodontal tissues that will not only affect the whole quadrant in question, but may even be disseminated to other parts of the body.[31] A single blinded investigator, who had no knowledge of whether the sections were experimental or control, performed the analysis.

Statistical Analysis

The Mann-Whitney test was used for statistical analysis, with the level of significance set at 5%, using the implants as well as the dogs as experimental units.

RESULTS

Clinical Findings

In phase I (first 3 months), periodontal infection was successfully induced on the experimental side (Fig 2a), with the presence of deep periodontal pockets as well as bleeding on probing and exudation after soft tissue compression. Bone loss and furcation involvement were observed radiographically (Fig 2b) on the experimental side. The control side had normal periodontal structures (Fig 2c).

Based on these findings, phase II began with extraction of the teeth. Figure 3a depicts the control teeth and Fig 3b the experimental teeth. After

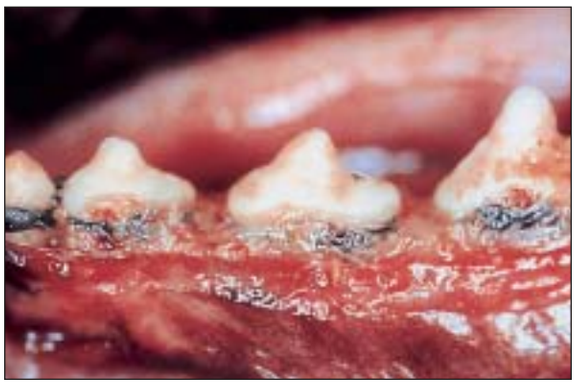

Fig 2a Plaque accumulation during the 3 months of phase I on the experimental side.

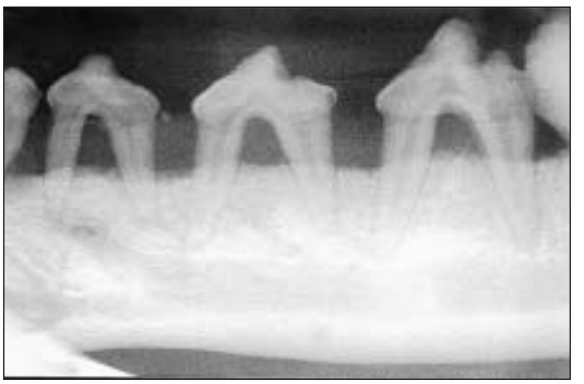

Fig 2b Radiographic aspect of experimental teeth after 3 months of phase I. Note bone loss in bifurcation and interproximal areas, indicating presence of periodontal disease.

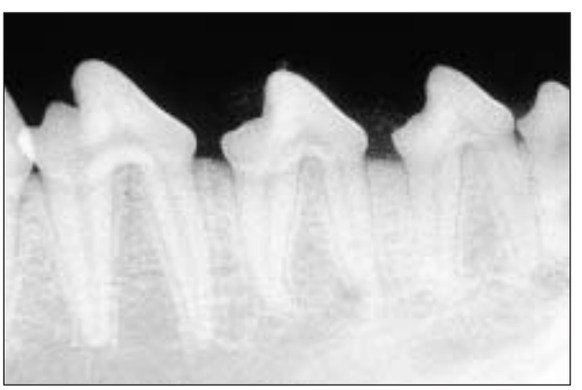

Fig 2c Radiographic aspect of control teeth after phase I. Good quality bone is apparent, and there is no evidence of radiolucencies.

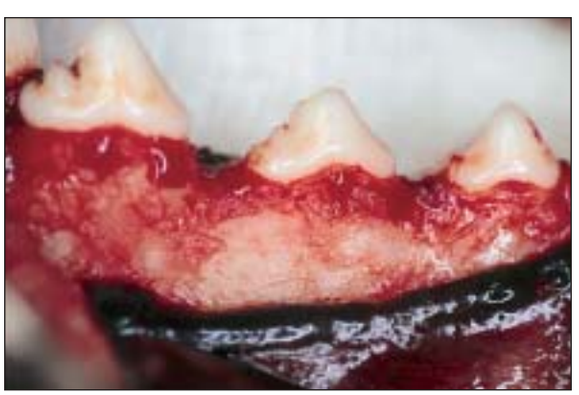

Fig 3a Clinical aspect of control side at the time of extraction. Normal levels of alveolar bone can be seen.

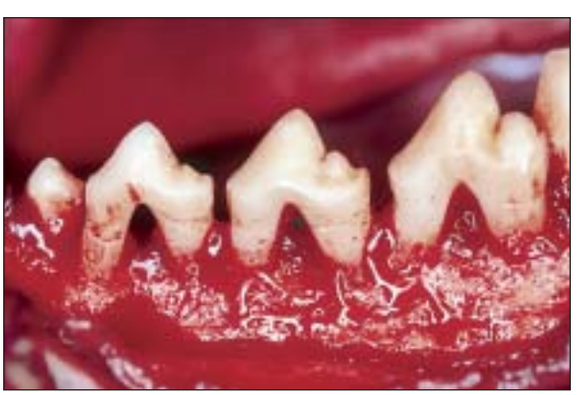

Fig 3b Clinical aspect of teeth at extraction on experimental side after cleaning and removal of granulation tissue to demonstrate the bifurcation and bone loss.

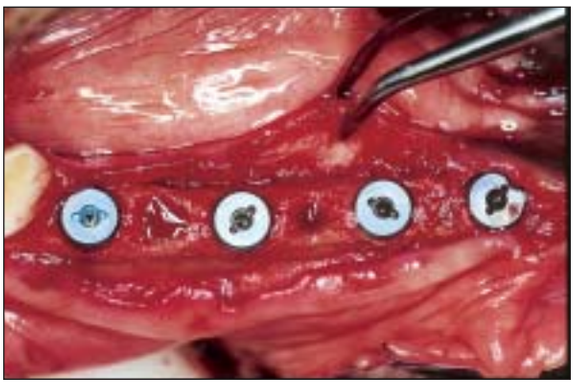

Fig 4 Immediate implantation of root-analog implants after extraction of premolar teeth in dogs.

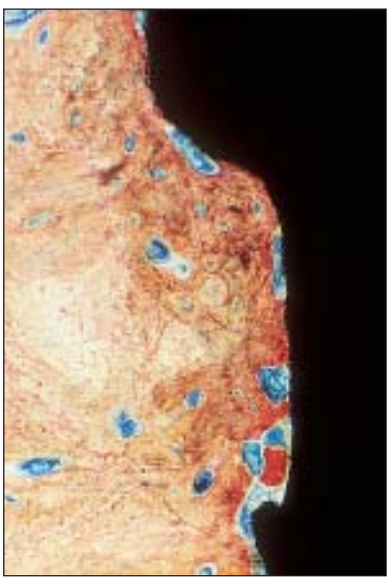

Fig 5a Photomicrograph (×50) showing bone *(orange)* in direct contact with implant *(black)* of the experimental group.

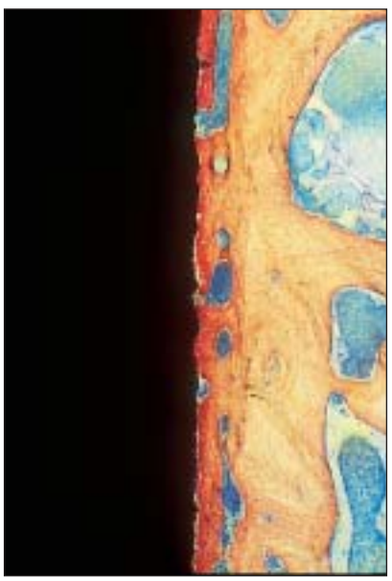

Fig 5b Photomicrograph (×125) showing bone *(orange)* in direct contact with implant *(black)* of the control group.

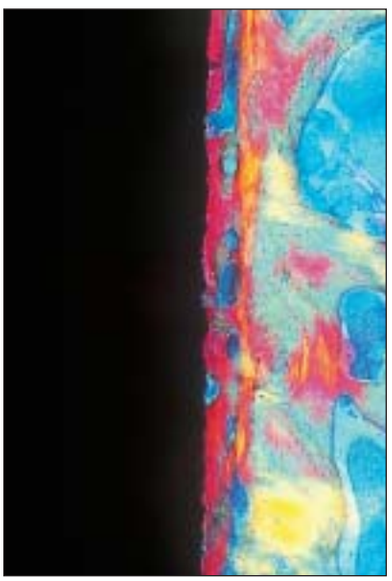

Fig 5c Photomicrograph (×125) of the same area, using polarized light microscopy.

extraction, implants were placed on both sides (Fig 4). Healing progressed uneventfully during the 12-week postoperative period, without significant inflammation or exudate on either the experimental or the control side. At the time of sacrifice, radiographic evaluation showed a loss of 3 implants in the experimental group and 5 implants in the control group. All other implants were clinically stable at the end of the experiment.

Histologic Observations

The bone-implant interface had mineralized bone matrix in intimate contact with the implant surface. The bone tissue was characterized by concentric or parallel lamellar formations. Trabecular spaces of different diameters were covered by endosteum, and at some points were in close contact with the implant surface.

Histomorphometric Findings

Histomorphometric analysis revealed small differences in the percentage of bone-implant contact (Figs 5a and 5b). Figure 5c shows the same structures as in Fig 5b with polarized light microscopy.

The mean percentage of direct bone-implant contact around the middle third of the experimental implants was 66.0 ± 19.6% (range 15.71% to 85.61%) and around the control implants was 62.4 ± 19.6% (range 21.18% to 88.52%). The difference was not statistically significant (Table 1; $P > .5$). When each dog was used as an experimental unit, the differences were also not statistically significant. This analysis indicated mean bone-implant contact in the control group of 61.71 ± 8.4% (range 53.09% to 76.35%) and in the experimental group 66.64 ± 9.61% (range 45.73% to 80.57%).

Table 1 Percentage of Bone-Implant Contact

Implant no.	Control group	Experimental group
1	79.2305	70.284
2	59.382	78.0525
3	76.291	56.663
4	60.867	47.6055
5	75.8265	65.347
6	36.7165	15.714
7	34.3905	85.406
8	21.182	79.428
9	88.521	78.8155
10	76.354	75.4855
11	77.297	77.748
12	56.9925	72.6085
13	75.07	74.1055
14	46.878	27.9235
15	70.379	57.047
16	—	85.612
17	—	74.7495
Mean	62.4	66.0
Median	70.4	74.1
SD	19.6	19.6

Mann-Whitney test (P = .597).

DISCUSSION

Different animals have been used to establish experimental periodontal disease with histologic, pathologic, and microbiologic characteristics similar to those of humans, including rats,[32,33] squirrel monkeys,[34] rhesus monkeys,[35] arctoides monkeys,[36] cynomolgus monkeys,[37–39] and ferrets.[40] It has thus been shown that the placement of silk ligatures at the gingival margin leads to plaque accumulation and marginal periodontitis, with loss of connective tissue attachment and loss of alveolar bone in all of these animals. The more commonly used animal is the dog, as cited in the following studies.

Dogs are susceptible to naturally occurring periodontal disease and experimental periodontitis, leading to alveolar bone loss. In dogs, periodontitis-associated plaque is easily induced,[41,42] and among the observed effects are enhanced subgingival plaque accumulation; a pronounced increase in gingival exudation; rapid formation of periodontal pockets; loss of alveolar bone, attachment, and tooth substance (resorption); and an apical displacement of the gingival margin.[43,44] The techniques used most often to induce this are the placement of an elastic band or a silk suture in the cementoenamel junction[45,46] or surgical creation of bone defects.[47,48] In the present study, both silk sutures and surgically created bone defects, in accordance with Schliephake and Kracht,[24] were used and resulted in a Class III furcation lesion, observed both clinically and radiographically.

Healing occurred without problems. However, at sacrifice, there was a loss of 3 implants in the experimental group and 5 implants in the control group. This may occur if the diameter of the distal alveolus of the fourth premolar is slightly larger than that of the implant used. In spite of the fact that there was initial vertical bone-implant contact in the present study, soft tissue may have migrated into the vacant spaces as a result of the smaller diameter of the implant. In addition, implant loss is considered a normal finding in animals, especially in dogs.[49–51]

For the histometric analysis, the middle third of the implants was analyzed[23,30] to intentionally avoid the cervical third (because of possible resorption of the bone crest[52–54]) and the apical third (because implants can closely approximate or slightly penetrate the superior wall of the inferior alveolar canal); both are common findings in studies with dogs.

The percent of bone-implant contact in this study was 62.4% for control implants and 66.0% for experimental implants, which was not statistically significantly different. This percent of bone-implant contact is greater than the mean of 47.9% reported by Ettinger and associates,[55] who suggested that there can be a wide variation in bone-implant contact, depending on the quality of bone at any site and the remodeling process that is going on at the time. Implant surface characteristics may have positively influenced these results as suggested by Wong and coworkers.[56] They concluded in their paper that rough surfaces, such as the one used in this study, allow stronger early biomechanical retention with better bone-implant contact versus smooth surfaces.

Immediate implant placement has the advantage of preserving the height and width of the alveolar bone.[11,21,57–59] Thus, it is one more treatment option that can be used when the loss of teeth is inevitable because of periodontal disease, if bone loss caused by the disease is not so dramatic as to prevent implant support. According to Lazzara,[3] one of the main diagnostic parameters that must be considered when evaluating a patient for dental implants is the amount of bone at the receptor site. Both the vertical height and the buccolingual bone dimensions must be considered in determining whether an endosseous implant can be placed. With these parameters, immediate implantation in cases of periodontal disease can be possible, safe, and easy, with results similar to those in disease-free sites.

SUMMARY

The objective of this study was to evaluate the extent of bone-implant contact of implants placed in alveoli immediately after extraction of teeth with periodontal disease. In this animal population, the results of this study support the conclusion that periodontally infected sites may not be a contraindication for immediate implants, if appropriate antibiotics are administered preoperatively and postoperatively, and if meticulous cleansing and debridement of the alveoli are performed before implant placement, as described by Novaes Jr and Novaes[17] and Novaes and coworkers.[23]

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REFERENCES

1. Schulte W. The intra-osseous Al_2O_3 (Frialit) Tuebingen implant. Developmental status after eight years (II). Quintessence Int 1984;15:19–35.
2. Anneroth G, Hedström KG, Kjellman O, Köndell P-Å, Nordenram Å. Endosseous titanium implants in extraction sockets. An experimental study in monkeys. Int J Oral Surg 1985;14:50–55.
3. Lazzara RJ. Immediate implant placement into extraction sites: Surgical and restorative advantages. Int J Periodontics Restorative Dent 1989;9:332–343.
4. Schulte W, d'Hoedt B, Axmann D, Gomez G. 15 Jahre Tübinger Implantat und seine Weiterentwicklung zum Frialit-2 System. Z Zahnärztl Implantol 1992;VIII,77–96.
5. Novaes AB Jr, Novaes AB. IMZ implants placed into extraction sockets in association with membrane therapy (Gengiflex) and porous hydroxyapatite: A case report. Int J Oral Maxillofac Implants 1992;7:536–540.
6. Novaes AB Jr, Novaes AB. Bone formation over a TiAl6V4 (IMZ) implant placed into an extraction socket in association with membrane therapy (Gengiflex). Clin Oral Implants Res 1993;4:106–110.
7. Gomez-Roman G, Schulte W, d'Hoedt B, Axman-Krcmar D. The Frialit-2 implant system: Five-year clinical experience in single-tooth and immediately postextraction applications. Int J Oral Maxillofac Implants 1997;12:299–309.
8. Krump JL, Barnett BG. The immediate implant: A treatment alternative. Int J Oral Maxillofac Implants 1991;6: 19–23.
9. Barzilay I, Graser GN, Iranpour B, Natiella JR. Immediate implantation of a pure titanium implant into an extraction socket: Report of a pilot procedure. Int J Oral Maxillofac Implants 1991;6:277–284.
10. Schwartz-Arad D, Chaushu G. The ways and wherefores of immediate placement of implants into fresh extraction sites: A literature review. J Periodontol 1997;68:915–923.
11. Parr GR, Steflik DE, Sisk AL. Histomorphometric and histologic observations of bone healing around immediate implants in dogs. Int J Oral Maxillofac Implants 1993;8: 534–540.
12. Barzilay I, Graser GN, Iranpour B, Natiella JR, Proskin HM. Immediate implantation of pure titanium implants into extraction sockets of *Macaca fascicularis.* Part II: Histologic observations. Int J Oral Maxillofac Implants 1996;11:489–497.
13. Wong K. Immediate implantation of endosseous dental implants in the posterior maxilla and anatomic advantages for this region: A case report. Int J Oral Maxillofac Implants 1996;11:529–533.
14. Brägger U, Hämmerle CHF, Lang NP. Immediate transmucosal implants using the principle of guided tissue regeneration (II). A cross-sectional study comparing the clinical outcome 1 year after immediate to standard implant placement. Clin Oral Implants Res 1996;7:268–276.
15. Watzek G, Haider R, Mensdorff-Pouilly N, Haas R. Immediate and delayed implantation for complete restoration of the jaw following extraction of all residual teeth: A retrospective study comparing different types of serial immediate implantation. Int J Oral Maxillofac Implants 1995;10:561–567.
16. Barzilay I. Immediate implants: Their current status. Int J Prosthodont 1993;6:169–175.
17. Novaes AB Jr, Novaes AB. Immediate implants placed into infected sites: A clinical report. Int J Oral Maxillofac Implants 1995;10:609–613.
18. Novaes AB Jr, Novaes AB. Soft tissue management for primary closure in guided bone regeneration: Surgical technique and case report. Int J Oral Maxillofac Implants 1997; 12:84–87.
19. Becker W, Becker BE. Guided tissue regeneration for implants placed into extraction sockets and for implant dehiscences: Surgical techniques and case reports. Int J Periodontics Restorative Dent 1990;10:377–391.
20. Tolman DE, Keller EE. Endosseous implant placement immediately following dental extraction and alveoloplasty: Preliminary report with 6-year follow-up. Int J Oral Maxillofac Implants 1991;6:24–28.
21. Werbitt MJ, Goldberg PV. The immediate implant: Bone preservation and bone regeneration. Int J Periodontics Restorative Dent 1992;12:207–217.
22. Wilson TG Jr. Guided tissue regeneration around dental implants in immediate and recent extraction sites: Initial observations. Int J Periodontics Restorative Dent 1992;12: 185–193.
23. Novaes AB Jr, Vidigal GM Jr, Novaes AB, Grisi MFM, Polloni S, Rosa A. Immediate implants placed into infected sites: A histomorphometric study in dogs. Int J Oral Maxillofac Implants 1998;13:422–427.
24. Schliephake H, Kracht D. Vertical ridge augmentation using polylactic membranes in conjunction with immediate implants in periodontally compromised extraction sites: An experimental study in dogs. Int J Oral Maxillofac Implants 1997;12:325–334.
25. Donath K, Breuner G. A method for the study of undecalcified bones and teeth with attached soft tissues. J Oral Pathol 1982;11:318–326.

26. Caudill RF, Meffert RM. Histologic analysis of the osseointegration of endosseous implants in simulated extraction sockets with and without e-PTFE barriers. Part I. Preliminary findings. Int J Periodontics Restorative Dent 1991;11: 207–215.
27. Lekholm U, Becker W, Dahlin C, Becker B, Donath K, Morrison E. The role of early versus late removal of GTAM membranes on bone formation al oral implants placed into immediate extraction sockets. An experimental study in dogs. Clin Oral Implants Res 1993;4:121–129.
28. Parr JA, Young T, Dunn-Jena P, Garetto LP. Histomorphometrical analysis of the bone-implant interface: Comparison of microradiography and bright-field microscopy. Biomaterials 1996;17:1921–1926.
29. Terheyden H, Jepsen S, Möller B, Tucker MM, Rueger DC. Sinus floor augmentation with simultaneous placement of dental implants using a combination of deproteinized bone xenografts and recombinant human osteogeneic protein-1. A histometric study in miniature pigs. Clin Oral Implants Res 1999;10:510–521.
30. Evans GH, Mendez AJ, Caudill RF. Loaded and nonloaded titanium versus hydroxylapatite-coated threaded implants in the canine mandible. Int J Oral Maxillofac Implants 1996; 11:360–371.
31. Page RC. The pathobiology of periodontal diseases may affect systemic diseases: Inversion of a paradigm. Ann Periodontol 1998;3:108–120.
32. Klausen B. Microbiological and immunological aspects of experimental periodontal disease in rats: A review article. J Periodontol 1991;62:59–73.
33. Györfi A, Fazekas A, Suba Z, Ender F, Rosivall L. Neurogenic component in ligature-induced periodontitis in the rat. J Clin Periodontol 1994;21:601–605.
34. Kennedy JE, Polson AM. Experimental marginal periodontitis in squirrel monkeys. J Periodontol 1973;44:140–144.
35. Caton JG, Zander HA. Primate model for testing periodontal treatment procedures: I. Histologic investigation of localized periodontal pockets produced by orthodontic elastics. J Periodontol 1975;46:71–77.
36. Slots J, Hausmann E. Longitudinal study of experimentally induced periodontal disease in *Macaca arctoides:* Relationship between microflora and alveolar bone loss. Infect Immun 1979;23:260–269.
37. Kornman KS, Holt SC, Robertson PB. The microbiology of ligature-induced periodontitis in the cynomolgus monkey. J Periodontal Res 1981;16:363–371.
38. Brecx MC, Nalbandian J, Ooya K, Kornman KS, Robertson PB. Morphological studies on periodontal disease in the cynomolgus monkey. II. Light microscopic observations on ligature-induced periodontitis. J Periodontal Res 1985;20: 165–175.
39. Nemeth E, Kulkarni GW, McCulloch CAG. Disturbances of gingival fibroblast population homeostasis due to experimentally induced inflammation in the cynomolgus monkey *(Macaca fascicularis):* Potential mechanism of disease progression. J Periodontal Res 1993;28:180–190.
40. Fischer RG, Klinge B. Clinical and histological evaluation of ligature-induced periodontitis in the domestic ferret. J Clin Periodontol 1994;21:230–239.
41. Lindhe J, Hamp S-E, Löe H. Experimental periodontitis in the beagle dog. J Periodontal Res 1973;8:1–10.
42. Ericsson I, Lindhe J, Rylander H, Okamoto H. Experimental periodontal breakdown in the dog. Scand J Dent Res 1975;83:189–192.
43. Schroeder HE, Lindhe J. Conversion of stable established gingivitis in the dog into destructive periodontitis. Arch Oral Biol 1975;20:775–782.
44. Giargia M, Ericsson I, Lindhe J, Berglundh T, Neiderud A-M. Tooth mobility and resolution of experimental periodontitis. An experimental study in the dog. J Clin Periodontol 1994;21:457–464.
45. Lindhe J, Ericsson I. Effect of ligature placement and dental plaque on periodontal tissue breakdown in the dog. J Periodontol 1978;49:343–350.
46. Schroeder HE, Lindhe J. Conditions and pathological features of rapidly destructive, experimental periodontitis in dogs. J Periodontol 1980;51:6–19.
47. Nishimura K, Noguchi Y, Yamada M, Shigeyama Y, Yamasaki A, Yamaoka A. Experimental periodontitis. J Osaka Dent Univ 1987;21:81–85.
48. Al-Ali W, Bissada NF, Greenwell H. The effect of local doxycycline with and without tricalcium phosphate on the regenerative healing potential of periodontal osseous defects in dogs. J Periodontol 1989;60:582–590.
49. Zarb GA, Symington JM. Osseointegrated dental implants: Preliminary report on a replication study. J Prosthet Dent 1983;50:271–276.
50. Barzilay I, Graser GN, Iranpour B, Proskin HM. Immediate implantation of pure titanium implants into extraction sockets of *Macaca fascicularis.* Part I: clinical and radiographic assessment. Int J Oral Maxillofac Implants 1996;11:299-310.
51. Rosenquist B, Grenthe B. Immediate placement of implants into extraction sockets: Implant survival. Int J Oral Maxillofac Implants 1996;11:205–209.
52. Block MS, Kent JN, Kay JF. Evaluation of hydroxylapatite-coated titanium dental implants in dogs. J Oral Maxillofac Surg 1987;45:601–607.
53. Gammage DD, Bowman AE, Meffert RM, Cassingham RJ, Davenport WA. Histologic and scanning electron micrographic comparison of the osseous interface in loaded IMZ and Integral implants. Int J Periodontics Restorative Dent 1990;10:124–135.
54. Weber HP, Buser D, Donath K, et al. Comparison of healed tissues adjacent to submerged and non-submerged unloaded titanium dental implants. A histometric study in beagle dogs. Clin Oral Implants Res 1996 Mar;7:11–19.
55. Ettinger RL, Spivey JD, Han D-H, Koorbusch GF. Measurement of the interface between bone and immediate endosseous implants: A pilot study in dogs. Int J Oral Maxillofac Implants 1993;8:420–427.
56. Wong M, Eulenberger J, Schenk R. Effect of surface topology on the osseointegration of implant materials in trabecular bone. J Biomed Mater Res 1995;29:1567–1575.
57. Ashman A. An immediate tooth root replacement: An implant cylinder and synthetic bone combination. J Oral Implantol 1990;16:28–38.
58. Gelb DA. Immediate implant surgery: Three-year retrospective evaluation of 50 consecutive cases. Int J Oral Maxillofac Implants 1993;8:388–399.
59. Knox R, Lee K, Meffert R. Placement of hydroxyapatite-coated endosseous implants in fresh extraction sites: A case report. Int J Periodontics Restorative Dent 1993;13:245–253.